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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,143	11/17/2003	Rajiv Shah	047711-0325	1899

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EXAMINER	
PAK, YONG D	
ART UNIT.	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,143	SHAH ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 10//035,918.

The amendment filed on October 23, 2006, amending claims 2 and 6-10, has been entered.

Claims 1-18 are pending. Claim 18 is withdrawn. Claims 1-17 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on October 23, 2006, have been fully considered and are deemed to be persuasive to overcome some of the objection/rejections previously applied.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-10 and claims 11-18 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-10 recite the phrase "predefined, desired functionality". The metes and bounds of this phrase in the context of the above claims are not clear to the Examiner. A perusal of the specification did not provide the Examiner with a specific definition for

the above phrase. Therefore, it is not clear to the Examiner either from the specification or from the claim as to what specific "functions" of glucose oxidases are encompassed in the phrase "predefined, desired functionalities". Examiner requests clarification of the above term.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that the specification on page 12, paragraph [0038], describes an example of a "desired functionality" and therefore, the claims are not indefinite. Examiner respectfully disagrees. The specification on page 12, paragraph [0038], does not provide a specific definition for the phrase, but only gives one example of a "predefined, desired functionality". Therefore, the metes and bounds of the functionalities encompassed by the above phrase are not clear.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Hatzinikolaou et al. and Stemmer.

Claims 1-3 and 7-8 are drawn to a method of formulating glucose oxidases by obtaining an organism, such as an *E. coli*, with glucose oxidase genes, growing colonies of the organism, altering the environment of the colonies, such as introducing peroxide, screening the colonies to identify colonies with active glucose oxidase for a predefined, desired functionality, such as use in glucose sensors, and determining whether the colonies grown in the presence of peroxide are active.

Valdes et al. (form PTO-892) discloses that glucose oxidase in glucose sensors are degraded by peroxide and this "decay can lead to the eventual failure of the senor" (abstract and page 367). Valdes et al. teaches that to ensure longer sensor functionality, instead of replacing the sensor with fresh enzyme, as has been practiced in the art, techniques to "prevent the degradation of the enzyme" is advantageous (page 375). With this teaching at hand, one having ordinary skill in the art would have concluded that degradation of glucose oxidase in a sensor may be prevented by using

chemical agents, as suggested by Valdes et al., or to use glucose oxidase mutants that are resistant to peroxide degradation, since methods of generating mutants having resistance to chemicals are known in the art, as discussed below. Valdes et al. also teaches a method of determining activity of glucose oxidase (page 370).

The difference between the reference of Valdes et al. and the instant invention is that the reference of Valdes et al. does not teach a method of producing and formulating active glucose oxidase from colonies grown in the presence of peroxide. However, there are many methods widely available in the art of creating mutant genes and screening for mutants displaying desired functional properties, such as having resistance to a chemical, such as a peroxide.

Hatzinikolaou et al. (form PTO-892) discloses a library of glucose oxidase genes known in the art, such as *A. Niger* (page 371).

Stemmer (US Patent 6,117,679 – form PTO-892) discloses a method of producing mutant enzymes by obtaining a library of genes of interest, creating a library of mutated genes by multiple cycles (at least 2-6 cycles) of PCR, error-prone PCR and/or gene shuffling (abstract, Column 4-11 and Column 22). In the method of Stemmer, each mutated genes are introduced into separate expression vectors, which are then inserted into *E. coli* (Column 25, 31-32). Stemmer teaches these host cells are then tested for the presence of desired mutations, such as growing the cells or colony under selective pressure and isolating the protein and testing of the protein encoded for activity (Column 32). Stemmer teaches a method of screening for colonies having

resistance to a chemical by plating transformed cells comprising mutated genes onto agar plates having varying concentrations of said chemical (Column 78).

Therefore, combining the teachings of Valdes et al., Hatzinikolaou et al. and Stemmer, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to formulate or produce glucose oxidases having resistance to peroxide by generating a library of mutated genes using the glucose oxidase gene of Hatzinikolaou et al. and the method of Stemmer, transforming *E. coli* with vectors comprising each of the mutated genes, growing colonies of said cells in the presence of peroxide and determining whether the colonies have active glucose oxidase. One of ordinary skill in the art would have been motivated to do so in order to generate active glucose oxidases that are resistant to peroxide. One of ordinary skill in the art would have been motivated to produce mutant peroxide resistant glucose oxidases in order to use them in glucose sensors, thereby prolonging their use, since Valdes et al. teaches that glucose oxidases in glucose sensors are degraded by peroxide, leading to failure of the sensor. One of ordinary skill in the art would have had a reasonable expectation of success since Hatzinikolaou et al. teaches glucose oxidase genes and Stemmer teaches a method of generating a library of mutant genes and screening for activity and other desired properties, such as resistance to a chemical.

Therefore, the above references render claims 1-3 and 7-8 *prima facie* obvious.

Claims 4-6 and 9-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Stemmer and Hatzinikolaou et al. as applied to claims 1-3 and 7-8 above, and further in view of Wagner and Aldrich Catalog.

Claims 4-6 and 9-17 are drawn to a method of formulating or producing glucose oxidases an organism with glucose oxidase genes, growing colonies of the organism, altering the environment of the colonies, such as introducing peroxide, screening the colonies to identify colonies with active glucose oxidase and determining whether the colonies grown in the presence of peroxide are active by testing glucose oxidase in sensors and using fluorescence of a leuco-cryalsta-violet.

Valdes et al., Stemmer and Hatzinikolaou et al. in combination teach a method of formulating or producing mutant glucose oxidases, as discussed above. Hatzinikolaou et al. also discloses a method of isolating and purifying glucose oxidase as recited in the claims and methods of measuring glucose oxidase activity (pages 372-373).

The difference between the reference of Valdes et al., Stemmer and Hatzinikolaou et al. and the instant invention is that said references do not teach a method of determining whether the colonies contain active glucose oxidase by testing glucose oxidase in sensors and using fluorescence.

Wagner (EP 0 251 475 A1 - form PTO-892) discloses a method of determining glucose oxidase activity via a sensor by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission (pages 2-3). In the method of Wagner, the glucose oxidase is conjugated to a

dye and immobilized in the sensor (page 3). Wagner also teaches that any fluorescent dye sensitive to quenching of its fluorescence emission by oxygen can be used (page 5). Aldrich Catalog (form PTO-892) discloses a leuco-cryalsta-violet dye (page 1005), as one such dye.

Therefore, combining the teachings of Valdes et al., Stemmer and Hatzinikolaou et al., Wagner and Aldrich Catalog, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the method of Wagner to ascertain activity of the glucose oxidase, wherein glucose oxidase is isolated and purified by the method taught by Hatzinikolaou et al. One of ordinary skill in the art would have been motivated to do so in order to determine whether the colonies comprising mutated glucose oxidases have active glucose oxidase. One of ordinary skill in the art would have had a reasonable expectation of success since Wagner teaches how to determine activity of glucose oxidase by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the fluorescence emission.

Therefore, the above references render claims 4-6 and 9-17 *prima facie* obvious.

In response to the previous Office Action, applicants have traversed the above two rejections together. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that Examiner acknowledges that Valdes et al. does not teach a method of producing mutant glucose oxidase that is resistant to degradation from

peroxide, but that Valdes et al. teaches a different procedure, wherein chemical agents are used to address peroxide degradation. While it is true that Valdes et al. does not teach a method of producing a library of mutated glucose oxidase genes, Valdes et al. does teach that another option of addressing the peroxide degradation of glucose oxidase is to "prevent the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph). With this teaching at hand, one having ordinary skill in the art would conclude that glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use "other techniques" such as produding glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are known in the art, as taught by Stemmer.

Applicants also argue that Valdes does not teach or suggest the features of the present invention but also teaches away from the present invention because Valdes refers to conventional, known "additive" methods for addressing peroxide degradation of glucose oxidase. Examiner respectfully disagrees. First, Valdes et al. does not teach away from the claimed method. Valdes et al. in fact provides the basic foundation for this instant invention. Valdes et al. teaches that degradation of glucose oxidase in sensors can be addressed by preventing "the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph). "[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw there from." (MPEP 2144.01). Although the reference does not explicitly teach making mutated glucose oxidase genes, one skilled in the art would

have inferred from Valdes et al. to use any or all prevailing methods to prevent degradation of glucose oxidase in glucose sensors such as by using chemical agents or to make glucose oxidases that are resistant to peroxide because Valdes et al. teaches that another option of addressing the peroxide degradation of glucose oxidase is to "prevent the degradation of the enzyme" (page 375, left paragraph). With this teaching at hand, one having ordinary skill in the art would conclude that degradation of glucose oxidase may be prevented by using chemical agents, as suggested by Valdes et al. or to use glucose oxidase mutants that are resistant to peroxide since methods of generating mutants having resistance to chemicals are well known and practiced by others in the art, as taught by Stemmer.

Also, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The reference of Valdes et al. is relied upon for its fundamental teaching of addressing the degradation of glucose oxidase by preventing "the degradation of the enzyme using other chemical agents or, techniques" (page 375, left paragraph), such as making mutated glucose oxidase genes that encode glucose oxidases that are resistant to peroxide degradation. The reference of Stemmer and Hatzinikolaou et al. provides teaching on a method of generating mutant glucose oxidases.

Applicants also argue that none of the reference provides suggestions or motivation for formulating a glucose oxidase enzyme by "creating a library of mutated

glucose oxidase genes' or mutating glucose oxidases. Examiner respectfully disagrees. MPEP 2144 states that

> "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law." and
>
> "The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination."

In the instant case, although the reference may not explicitly teach making mutated glucose oxidase genes, one skilled in the art would have been reasonably led to conclude to prevent degradation of glucose oxidase in glucose sensors by making mutant glucose oxidases that are resistant to peroxide because methods of mutagenizing an enzyme to become resistant against a chemical is well known in the art, as taught by Stemmer.

Applicants also argue that Valdes et al. refers to completely different directions taken by those most skilled in the art, whereby the glucose oxidase enzyme is immobilized and attached to a support that deactivates peroxide. Examiner respectfully disagrees. As discussed above, Valdes et al. provides an alternate direction to address the degradation of glucose oxidase. With this teaching at hand, one having ordinary

skill in the art would look at alternative methods for making a glucose oxidase that is resistant to peroxide.

Applicants argue that one skilled in the art would not have been motivated to select a process as described by Stemmer, to make such a drastic change in the direction taken by those most skilled in the prior art as described by Valdes et al., which employes addition of additives. Examiner respectfully disagrees. Valdes et al. does not limit preventing degradation of glucose oxidase by only adding chemical agents, but teaches that degradation of glucose oxidase can be addressed by using other techniques which encompass a method of obtaining a peroxide resistant enzyme through mutagenesis. As discussed above, one having ordinary skill in the art would have recognized to apply such "other techniques", such as mutagenizing the enzyme, thus eliminating the root of the problem, not necessitating addition of chemicals. One having ordinary skill in the art would have looked to mutating glucose oxidase genes that are resistant to hydrogen peroxide because Valdes et al. teaches that additives, such as catatalse is inactivated by hydrogen peroxide, which would be limited in preventing degradation of glucose oxidase. Instead of adding additives that neutralizes the effects of hydrogen peroxide, one having ordinary skill in the art would have recognized to solve the problem of glucose oxidase degradation by peroxide by making glucose oxidase mutants that are resistant to hydrogen peroxide.

Hence both of the rejections under 35 USC 103(a) are maintained.

None of the claims are allowable.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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